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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Syken et al.	Group Art Unit: 1632
Serial No.: 09/908,992	Examiner: Li, Q.
Filing Date: July 19, 2001	Attorney Docket No.: HMV-054.01
For: <i>Methods and Reagents to Regulate Apoptosis</i>	

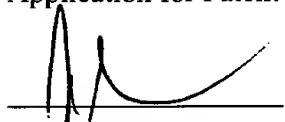
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22312-1450

**Declaration of J. Syken and K. Münger under 37 C.F.R. § 1.132**

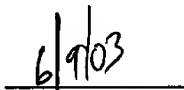
Sir:

1. We, Joshua Syken, a citizen of the United States, residing at 19 Goldsmith Street, Jamaica Plain, Massachusetts and Karl Münger, a citizen of the Switzerland, residing at 33 Goddard Street, Newton, Massachusetts, hereby declare as follows:
2. I, Joshua Syken, Ph.D., am a Postdoctoral fellow, Department of Neurobiology, Harvard Medical School, Boston, Massachusetts. A copy of my curriculum vitae and list of publications are attached hereto as Exhibit A.
3. I, Karl Münger, Ph.D., am an Associate Professor, Department of Pathology, Harvard Medical School, Boston, Massachusetts. A copy of my resume and list of publications are attached hereto as Exhibit B.
4. We are co-inventors in the above-referenced patent application.
5. We understand that the publication Syken et al. (Proc. Natl. Acad. Sci. U.S.A. 96:8499-8504 (1999)) was cited against the above-referenced patent application.
6. We are the sole inventors of the experimental work described in Syken et al, *supra*.
7. Dr. Tali De-Medina, Ph.D., coauthor of Syken et al., *supra*, is not a co-inventor in the above-referenced application. Dr. De-Medina performed experiments confirming our initial observation that Tid1S localized to the mitochondria. Accordingly, Dr. De-Medina did not contribute to our invention as set forth in this patent application.
8. We declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further, that these

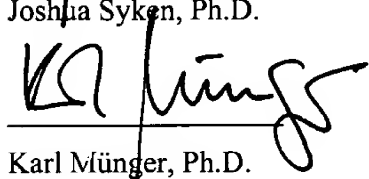
statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.



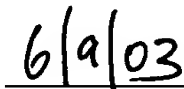
Joshua Syken, Ph.D.



Date



Karl Münger, Ph.D.



Date

Josh Syken, Ph.D.  
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#### Education/Research Experience

1992-1995  
B.S., Purchase College, Purchase NY  
Advisor: Dr. Elysse Craddock

1995-1999  
Ph.D., Harvard Medical School  
Advisor: Dr. Karl Munger  
Thesis: TID1 Encodes Two Mitochondrial Modulators of Apoptosis with Opposing Functions

2000-Present  
Postdoctoral fellow  
Harvard Medical School  
Advisor: Dr. Carla Shatz

#### Awards and Honors

1992 - CRC Chemistry Award, Purchase College  
1992-1995 - William D. Schlutow Scholarship for Excellence in Biology,  
Purchase College.  
1995 - Purchase College Presidents Achievement Award  
1995 - Summa Cum Laude, Purchase College  
1997-1999 - Ryan Fellow, Harvard Medical School  
2000-Present - NIH NRSA Postdoctoral Fellowship

#### Publications

Schilling B, De-Medina T, Syken J, Vidal M, Munger K. 1998. A novel human DnaJ protein, hTid-1, a homolog of the Drosophila tumor suppressor protein Tid56, can interact with the human papillomavirus type 16 E7 oncoprotein. Virology. 1998 247(1):74-85

Syken J, De-Medina T, Munger K., 1999  
TID1, a human homolog of the Drosophila tumor suppressor l(2)tid, encodes two mitochondrial modulators of apoptosis with opposing functions. Proc Natl Acad Sci U S A. 96(15):8499-504

Syken, J., Macian, F., Agarwal, S., Rao, A., Munger, K., 2003. TID1, a Mammalian Homolog of the Drosophila Tumor Suppressor lethal(2) tumorous imaginal discs Regulates Activation-Induced Cell Death in Th2 Cells. Oncogene, In Press.

## CURRICULUM VITAE

### PART I: General Information

**DATE PREPARED:** June 5, 2003

**Name:** Karl Munger

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**Place of Birth:** Zurich, Switzerland

#### **Education:**

1981      B.Sc. (Biochemistry), University of Zurich, Switzerland

1986      Ph. D. (Biochemistry), University of Zurich, Switzerland

#### **Postdoctoral Training:**

1986-1990      Viral Oncology, Laboratory of Tumor Virus Biology, National Cancer  
Institute, NIH, Bethesda, MD

#### **Professional Appointments:**

1990-1993      Visiting Associate, Laboratory of Tumor Virus Biology, National Cancer  
Institute, NIH, Bethesda, MD

1993-present      Member, Board of Tutors in Biochemical Sciences, Department of  
Molecular and Cellular Biology, Harvard University, Cambridge, MA.

1993 –1998      Assistant Professor, Department of Pathology, Harvard Medical School,  
Boston, MA

1998-present      Associate Professor, Department of Pathology, Harvard Medical School,  
Boston, MA

**Other Professional Positions and Major Visiting Appointments:**

1995	Consultant, WHO/IARC Working Group on Human Papillomaviruses
1995-1996	Faculty Member, Histopathobiology of Neoplasia Workshop, organized by the American Association for Cancer Research
1996	Visiting Professor, Department of Biology, University of Padua, Italy
1999	Consultant, Boston BioProducts, Inc., Ashland, MA
1999	Consultant, McKinsey and Company
2001-date	Consultant, National Toxicology Program, Evaluation of HPV as a Carcinogen
2002	Consultant, Pharmacia-Upjohn Company, Kalamazoo, MI.
2002	Faculty Member, Pathobiology of Cancer Workshop, organized by the American Association for Cancer Research
2002-present	Consultant, Arbor Vita Corporation, Sunnyvale CA

**Major Committee Assignments:**

1996	Temporary Member, Experimental Virology Study Section, National Institutes of Health
1996	Scientific Committee, 15th International Papillomavirus Workshop, Queensland, Australia 1996
1997	Temporary Member, Experimental Virology Study Section, National Institutes of Health
1998	Chairman, Viral Oncology Section, Program Committee, American Association for Cancer Research, Annual Meeting.
1998	Organizing Committee, International Conference on Small DNA Tumorviruses, Madison, WI.
1998	Member, NIH Special Emphasis Panel (ZRG5 EVR-01) Study Section
1998	Member, NIH Site Visit Committee for Program Project 1 P01 DE2704-01.
1998	Member, NIH Site Visit Committee for Program Project 1 P50 DC00203-15A1
1998-2001	Cancer Research Campaign (UK), Outside Reviewer
1999	Scientific Program Committee, 17th International Papillomavirus Workshop, Charleston, SC.
1999	Grant Reviewer, National Science Foundation of Austria
1998	Member, NIH Special Emphasis Panel (DE 98-008)
1999	Temporary Member, NIDCR Special Emphasis Panel
2000-2001	Review Board, NIGM/NIH Intramural Postdoctoral Fellowship Program (PRAT Fellowships)

- 2000, 2003 Grant Reviewer, Dutch Cancer Society.
- 2000 Organizing Committee, International Conference on Small DNA Tumorviruses, Madison, WI.
- 2000-date Member NIDCR Special Review Panel.
- 2000-date Tenure Reviewer for Tufts University (2), Case Western University, Cleveland OH, University of Massachusetts, The Hebrew University of Jerusalem (Israel)
- 2000-2004 Regular Member, NIH Study Section "Virology".
- 2001, 2003 Grant Reviewer, National Science Foundation, Austria.
- 2001 Grant Reviewer, Italian Association for Cancer Research
- 2001 Scientific Program Committee, 19th International Papillomavirus Workshop, Florianopolis, Brazil
- 2002 Grant Reviewer, Ohio Cancer Research Associates.
- 2002 Grant Reviewer, Sass Fellowship Foundation
- 2002, 2003 Grant Reviewer, Department of Veterans Affairs
- 2002 Member, NIDCD Special Review Panel 020628.
- 2002 Organizing Committee, International Conference on Small DNA Tumorviruses, Madison, WI.
- 2002 Grant Reviewer, Research Management Group, Linthicum Heights, MD
- 2002 Grant Reviewer, Cancer Research UK
- 2003 Nomination Committee, NIGM/NIH Intramural Postdoctoral Fellowship Program (PRAT Fellowships)
- 2003 Member, Viral Oncogenesis and Mechanisms Section of the Cellular, Molecular, and Tumor Biology Subcommittee of the Program Committee for the Annual Meeting of the American Association for Cancer Research.
- 2003 Member, NIH Site Visit Committee for Program Project 1 P01 CA16038-31
- 2004 Scientific Committee, 21<sup>st</sup> International Papillomavirus Conference

**Professional Societies:**

Swiss Society for Biochemistry  
 American Society for Microbiology  
 American Association for Cancer Research  
 American Society for Investigative Pathology  
 Boston Cancer Research Association (Massachusetts Section of the American Association for Cancer Research), Vice President 1997-1998; President 1998-1999  
 International Papillomavirus Society

**Community Service Related to Professional Work:**

- 2001 Mentor, Outside Researchers Session, Excellence Through Diversity Initiative,  
Doctoral Scholars Program, New England Board of Higher Education.
- 2003 Mentor, Minorities in Cancer Research Council of the AACR, Symposium:  
“Navigating the Road to a Successful Career in Cancer Research”

**Editorial Boards:**

- 1995-present Journal of Virology
- 1998-present Virology
- 2001-present Cancer Research; Associate Editor
- 2001-present Cancer Biology & Therapy; Associate Editor
- 2003-present Molecular Cancer

Ad hoc reviewer for: Am. J. Pathol., Biochemistry, Biochem. Biophys. Acta, Br. J. Cancer.,  
Cancer, Cancer Detection and Prevention, Cancer Invest., Cell, Cell Death  
Diff., Cell Growth Diff., Clin. Canc. Res., EMBO J., Exp. Cell Res., Gene,  
Genes & Development, Genes, Chromosomes and Cancer, Gynecol.  
Oncol., Int. J. Cancer, IUBMB Life, J. Cell Science., J. Clin. Invest., J.  
Clin. Oncol., J. Exp. Med, J. Immunol., J. Natl. Canc. Inst., Mol. Cell  
Biol., Mol. Pharmacol., Microbiol. Mol. Biol. Reviews., Nature, Nature  
Cell Biology, Nature Medicine, Nucl. Acids Res., Oncogene, Oncol. Res.,  
Proc. Natl. Acad. Sci. USA, Science, Trends in Microbiology, Virus Res.

**Awards and Honors:**

- 1986-1988 John E. Fogarty Postdoctoral Fellowship
- 1989 Advanced Training Fellowship, Swiss National Science Foundation
- 1990 Dr. Ernst Th. Jucker Award for Experimental Cancer Research, Zurich,  
Switzerland
- 1996-1998 Junior Faculty Research Award, American Cancer Society
- 1998-2000 Ludwig Scholar

**Funding**

**Past:**

- 1/94-12/94 Funds for Discovery; PI; “Disruption of dimer formation as a strategy to  
inactivate the HPV E7 oncoprotein.”
- 1/94-12/94 Milton Fund; PI; “Protein domains governing the transformation function of the  
HPV E7 oncoprotein.”
- 1/94-12/98 American Cancer Society; PI; “Characterization of cellular factors associated with  
the HPV E7 protein” (#VM97; #RPG-94-011-04-VM).

- 1/95-12/97 Council for Tobacco Research; PI; “Viral oncoproteins as probes to study cellular growth regulation” (#3859).
- 1/96-12/98 American Cancer Society; PI; “The role of HPV E7 in cervical carcinogenesis” (JFRA-597)
- 6/97-5/98 National Institutes of Health; PI; “The role of basic helix-loop-helix (bHLH) proteins in epithelial cell proliferation and differentiation”; Pilot and Feasibility Project Grant; P30 AR42689 (T.S. Kupper, PI).
- 4/99-3/00 GLAXO-WELLCOME Co., PI; “Alteration of Cellular Signal Transduction Pathways by the Human Papillomavirus E7 Oncoprotein”; Industry-sponsored Research Grant.
- 7/99-6/01 Hoechst Marion Roussel Co., “Modulation of TID1 During T-Cell Activation: Implications for Activation Induced Cell Death” Industry sponsored Research Grant.
- 4/98-3/03 Project leader; National Institutes of Health; “Cell cycle dysregulation in oral cancer”; Program Project Grant P01 DE012467 (David T. Wong, PI).

**Current:**

- 4/96-6/05 Principal Investigator: National Cancer Institute/National Institutes of Health; “Biological activity of HPV E7 in human epithelial cells” (R01 CA66980).
- 9/02-6/05 Principal Investigator: National Cancer Institute/National Institutes of Health; “Biological activity of HPV E7 in human epithelial cells”- Competitive Supplement (3R01CA066980-7S1)
- 2/00-1/05 Principal Investigator: National Cancer Institute/National Institutes of Health; “Modulation of Host Cell Apoptotic Responses by HPV E7” (R01 CA81135).
- 10/01-9/06 Project Co-investigator; National Heart, Lung, and Blood Institute/National Institutes of Health; “Adhesion molecules in transfusion biology” Program Project Grant 2P01 HL56949 (Denisa Wagner, P.I.).
- 7/02-6/03 Co-investigator: Stewart Trust; “Identification of cellular markers of human cervical preneoplasia by Serial Analysis of Gene Expression (SAGE)”
- 12/02-11/04 Principal Investigator: Astra-Zeneca; “Tripeptidyl transferase II and c-myc induced centrosome mediated genomic instability”
- 6/03-5/05 Co-Principal Investigator: CYTYC Corporation; “Cellular markers of cervical neoplasia
- 7/03-11/07 Project Co-investigator: National Cancer Institute/National Institutes of Health; “Spectroscopic imaging and diagnosis of neoplasia” Bioengineering Research Partnership CA097966-01; (Michael Feld, MIT, P.I.)



## Bibliography

### Original Articles:

1. M $\ddot{u}$ nger K, Lerch K, Tschierpe HJ. Metal accumulation in *Agaricus bisporus*: influence of Cd and Cu on growth and tyrosinase Activity. *Experientia* 38:1039-1041, 1982.
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3. M $\ddot{u}$ nger K, Germann UA, Lerch K. Isolation and structural organization of the *Neurospora crassa* copper metallothionein gene. *EMBO J.* 4:2665-2668, 1985.
4. M $\ddot{u}$ nger K, Lerch K. Copper metallothionein from the fungus *Agaricus bisporus*: chemical and spectroscopic properties. *Biochemistry* 24:6751-6756, 1985.
5. M $\ddot{u}$ nger K, Germann UA, Lerch K: The *Neurospora crassa* copper metallothionein gene: regulation of expression and chromosomal location. *J. Biol. Chem.* 262:7363-7367, 1987.
6. Moser R, Frey S, M $\ddot{u}$ nger K, Hehlhans T, Klausner S, Langen H, Winnacker E-L, Mertz R, Gutte B. Expression of the synthetic gene of an artificial DDT-binding polypeptide in *E. coli*. *Protein Engineering* 1:339-347, 1987.
7. M $\ddot{u}$ nger K, Lerch K. Peptide mapping of vertebrate and invertebrate metallothioneins. *Inorganica Chimica Acta* 151:11-13, 1988.
8. Phelps WC, Yee CL, M $\ddot{u}$ nger K, Howley PM. The human papillomavirus type 16 E7 gene encodes transactivation and transformation functions similar to adenovirus E1a. *Cell* 53:339-347, 1988.
9. Beltramini M, Giacometti GM, Salvato B, Giacometti G, M $\ddot{u}$ nger K, Lerch K. Luminescence emission from *Neurospora* copper metallothionein: Time-resolved Studies. *Biochem. J.* 260:189-193, 1989.
10. Dyson N, Howley PM, M $\ddot{u}$ nger K, Harlow, E. The human papillomavirus type 16 E7 oncoprotein is able to bind the retinoblastoma gene product. *Science* 243:934-937, 1989.
11. M $\ddot{u}$ nger K, Phelps WC, Bubbs V, Howley PM, Schlegel R. The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. *J. Virol.* 63:4417-4421, 1989.
12. M $\ddot{u}$ nger K, Werness BA, Dyson N, Phelps WC, Harlow E, Howley PM. Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. *EMBO J.* 8:4099-4105, 1989.
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22. Scheffner M, Munger K, Huibregtse JM, Howley PM. Targeted degradation of the retinoblastoma protein by a fusion of the human papillomavirus E6 and E7 oncoproteins. *EMBO J.* 11:2425-2431, 1992.
23. Dyson N, Guida P, Munger K, Harlow E. Homologous sequences in adenovirus E1A and human papillomavirus E7 proteins mediate interaction with the same set of cellular proteins. *J. Virol.* 66:6893-6902, 1992.
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25. Arbeit JM, Munger K, Howley PM, Hanahan D. Neuroepithelial carcinomas in mice transgenic with human papillomavirus Type 16 E6/E7 ORFs. *Am. J. Pathol.* 142:1187-1197, 1993.
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32. Jones DL, Alani RM, Munger, K. The human papillomavirus E7 oncoprotein can uncouple cellular differentiation and proliferation in human keratinocytes by abrogating p21Cip1-mediated inhibition of cdk2. *Genes & Development* 11:2101-2111, 1997.
33. Mavromatis KO, Jones DL, Muherjee R, Yee C, Grace M, Munger K. The carboxyl terminal zinc-binding domain of the human papillomavirus E7 protein can be functionally replaced by the homologous sequences of the E6 protein. *Virus Research* 52:109-118, 1997.
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35. Jones DL, Thompson, DA, Munger K. Destabilization of the pRB tumor suppressor protein and stabilization of p53 contribute to HPV type 16-induced apoptosis. *Virology* 239:97-107, 1997.
36. Schilling B, De-Medina T, Syken J, Vidal M, Munger K. A novel human DnaJ protein, hTid-1, a homolog of the Drosophila tumor suppressor protein Tid56, can interact with the human papillomavirus type 16 E7 oncoprotein. *Virology* 247:74-85, 1998.
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38. Timmermann S, Hinds PH, Munger K. Reexpression of endogenous p16ink4a in oral squamous cell carcinoma lines by 5-aza-2'-deoxycytidine induces a senescence-like state. *Oncogene* 17:3445-3453, 1998.
39. Jones DL, Thompson DA, Suh-Burgmann E, Grace M, Munger K. Expression of the HPV E7 oncoprotein mimics but does not evoke a p53-dependent DNA damage response pathway. *Virology*, 258:406-414, 1999.
40. Syken J, De-Medina T, Munger K. hTid-1, the human homolog of the Drosophila tumor suppressor Tid56, is a mitochondrial regulator of apoptosis. *Proc. Natl. Acad. Sci. USA* 96:8499-8506, 1999.
41. Alani RM, Hasskarl J, Grace M, Hernandez MC, Israel MA, Munger K. immortalization of primary human keratinocytes by the helix-loop-helix protein, Id1. *Proc. Natl. Acad. Sci. USA* 96:9637-9641, 1999.
42. Oettgen P, Kas K, Dube A, Gu X, Grall F, Thamrongsak U, Akbarali Y, Finger E, Boltax J, Endress G, Munger K, Kunsch C, Libermann TA. Characterization of ESE-2, a novel

- ESE-1-related ets transcription factor that is restricted to glandular epithelium and differentiated keratinocytes. *J. Biol. Chem.* 274:29439-29452, 1999.
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53. Eichten A, Westfall M, Pietenpol JA, Munger K: Stabilization and functional impairment of the tumor suppressor p53 by the human papillomavirus type 16 E7 oncoprotein, *Virology* 295:74-85, 2002

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55. Piboonniyom S, Duensing S, Swilling NW, Hasskarl J, Hinds PW, Munger K: Abrogation of the retinoblastoma tumor suppressor checkpoint during keratinocyte immortalization is not sufficient for induction of centrosome-mediated genomic instability, *Cancer Research* 63: 476-483, 2003
56. Genther SM, Sterling S, Duensing M, Munger K, Sattler C, Lambert PF: A quantitative role of the human papillomavirus type 16 E5 gene during the productive stage of the viral life cycle, *Journal of Virology* 77:2832-2842, 2003.
57. Basile JR, Eichten A, Zacny V, Munger K: NF- $\kappa$ B mediated induction of p21<sup>Cip1/Waf1</sup> by tumor necrosis factor  $\alpha$  induces growth arrest and cytoprotection in normal human keratinocytes, *Molecular Cancer Research* 1: 262-270, 2003.
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